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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,734	GEPSTEIN ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-186 and 196-199* is/are pending in the application.

4a) Of the above claim(s) *1-175, 182-186* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *176-181 and 196-199* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment to the abstract filed on April 19, 2007 has been received and entered. Applicant's amendment to the claims filed August 13, 2007 has been received and entered. Claims 1-186, 196-199 are pending in the application. Applicants have amended claims 176, 178-181, while claims 187-195 have been canceled. Applicants have also added claims 196-199.

Election/Restrictions

Applicant's election of claims 176-195 (group IV) in the reply filed on August 17, 2006 was acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicants also elected cardiac specific electrical activity for claims 177 and 189 for first action on merit.

Claims 1-175 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 17, 2006. It is noted that claims 182-185 and 190-193 were drawn to nonelected subject matter. Therefore, claims 182-185 were also withdrawn because they are drawn to non-elected species.

It is emphasized that claims 176-181, 196-199 will be examined to the extent claims are drawn to elected invention of an *in-vitro* culture of isolated human cells which will display substantial proliferation for at least as long as a time period selected from the range of 1-35 days, and which will predominantly display at least one characteristic associated with a cardiac phenotype of cardiac specific electrical activity for at least as long as a time period selected from the range of 1-60 days

would be examined in the instant application. Claims 176-181, 196-199 are under examination.

Withdrawn-Specification

The objection to the specification for reciting legal language "said" is withdrawn in view of amendments to the abstract.

Withdrawn-Claim Objections

The objection to the claim 179-181 for improper dependent claim is withdrawn in view of amendments to the claims.

Withdrawn-Claim Rejections - 35 USC § 112

Claims 176-181 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendments to the claim by removing the term substantial and slow from the claims.

Oath/Declaration

The Drs. Gepstein, Izhak Kehat, Itskovitz-Eldor and Amit declaration filed on April 19, 2007 under 37 CFR 1.132 filed is sufficient to overcome the rejection of claims176-181, 186-189 and 194-195 based upon the reference of Kehat et al (Circulation, Supplement II, Vol. 102 N0. 18, October 31, 2000, abstract IDS, applied under 35 U.S.C. 102(a).

The Drs. Gepstein, Izhak Kehat, Itskovitz-Eldor and Amit declaration filed on April 19, 2007 under 37 CFR 1.131 is sufficient to overcome the rejection of claims 176-177, 186-189 and 194-195 based upon the reference of Xu et al (US

2005/0164382A1, dated 7/28/2005, effective filing date 7/12/2001, applied under 35 U.S.C. 102(e).

The Dr. Amit declaration filed on April 19, 2007 under 37 CFR 1.132 is not sufficient to overcome the rejection of claims 176-177, 186-189 and 194-195 based upon the reference of Itskovitz-Eldor et al (Mol Med. 2000 Feb;6(2):88-95, IDS), applied under 35 U.S.C. 102(b).

New-Necessitated by amendments- Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 176-181, 196-199 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 176-181, 196-199 are vague and indefinite because claims are directed to an *in vitro* culture of an isolated human cell being in embryoid bodies. It is not apparent how cells could be considered isolated at the same time being in embryoid bodies. It is unclear if Applicants are claiming the isolated cells or the embryoid bodies. Embryoid bodies can be composed of many different cell types; therefore the metes and bounds of the claims are unclear. Claims 177-181, 196-198 and 199 directly on indirectly depend on claim 176. Appropriate correction is required.

Withdrawn-Claim Rejections - 35 USC § 102

Claims 176-181, 186-189 and 194-195 rejected under 35 U.S.C. 102(a) as being anticipated by Kehat et al (Circulation, Supplement II, Vol. 102 N0. 18,

October 31, 2000, abstract IDS) is withdrawn in view of declaration filed by Drs Gepstein, Izhak Kehat, Itskovitz-Eldor and Amit.

Claims 176-177, 186-189 and 194-195 rejected under 35 U.S.C. 102(e) as being anticipated by Xu et al (US 2005/0164382A1, dated 7/28/2005, effective filing date 7/12/2001) is withdrawn in view of declaration filed by Drs Gepstein, Izhak Kehat, Itskovitz-Eldor and Amit.

Maintained-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 176-177 remain rejected and newly added claims 196-199 are also rejected under 35 U.S.C. 102(b) as being anticipated by Itskovitz-Eldor et al (Mol Med. 2000 Feb;6(2):88-95, IDS).

Itskovitz-Eldor et al teach induction of expression of cell-specific genes during differentiation of the human ES cells into embryoid bodies (EB). It is noted that Itskovitz-Eldor et al disclose differentiation of human ES cell in myocardial linage that is induces development of pulsing muscle in EB (see page 92, col. 2, para 2). Itskovitz-Eldor et al also disclose a large vacuolated EB including cardiac muscle cell layer that is pulsing in synchronous rhythm (see Figure 4 A and B). It is further noted that Itskovitz-Eldor further characterizes the differentiated ES cell by dissociating EB with trypsin and plated cell on monolayer. Since, Itskovitz-Eldor et al taught an *in vitro* culture of human cell of cardio specific linage obtained from human ES cell that shows the cardiac specific synchronous rhythmic activity. The

cardio specific linage of human cell disclosed by Itskovitz-Eldor and those embraced by the instant claims appear to be structurally same, therefore, proliferation potential and other cardiac phenotype of these cells will be inherently present in the cells disclosed by Itskovitz-Eldor. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior ad products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433.

Where, in the instant cases, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to
product-by-process claims. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

Response to Arguments

Applicant's arguments filed on April 19, 2007 have been fully considered but they are not fully persuasive. Applicants in their argument point out that as amended claims have been amended to recite in vitro culture of isolated human cell being in plurality of EBs. In addition, applicants and well as the declaration by Dr. Amit asserts that cited reference was able to produce merely only one EB which

posses' cardiac synchronous rhythmic activity. Applicants argue that claims have now been amended to read over an *in vitro* culture comprising a plurality of embryoid bodies that exhibit cardiac phenotype.

In response it is noted that claim 176 has been amended to an *in vitro* culture of an isolated human cell being in plurality of EB wherein said EB showing at least one cardiac phenotype. These claims have been analyzed to the extent they read on elected invention of an in vitro culture of isolated human cell. Contrary to applicant's argument cited references teach in vitro hES culture in suspension in order to form plurality of EBs. The specification also teaches that twenty days after initiation of cellular aggregation 20–90% of the structures formed cystic EBs (Fig. 1B-I). Thus, it is apparent that contrary to applicant's argument cited reference teaches an isolated human cells being in plurality of cystic EB's. Furthermore, art also discloses rhythmic pulsation in "minority" of the cystic hEBs (see page 92, col. 2, para. 2, line7-8, emphasis added). It is emphasized the minority is defined as the smaller in number of two groups constituting a whole (see m-w.com/.). Examiner would agree with cited reference exemplified only one pulsing embryoid body, but clearly did not exclude cardiac phenotype in other population of EBs. However, the reference makes clear that there was a population (i.e., more than one EB) of pusling hEBs. One would reasonably conclude that the exemplified EB in Figure 4 is representation of the EBs discussed on page 92, 2nd col, 2nd paragraph. In fact, applicant's declaration compares the number of hES cell clone to number of EBs showing cardiac phenotype. The declaration fails to establish the fact that H9 clone of hES cells disclosed in cited reference contained only one EB showing cardiac phenotype. It is noted that declaration does not provide evidence that other EBs in H9 clone of hES cells would not have cardiac phenotype. MPEP 2113 states "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190

F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ430, 433 (CCPA 1977). Thus, Itskovitz-Eldor et al taught an *in vitro* culture of human cell being in plurality of EBs. The cited reference also exemplified a EB from the plurality of population of EB having cardiac specific synchronous rhythmic activity. The cardio specific linage of human cell disclosed by Itskovitz-Eldor and those embraced by the instant claims appear to be structurally same, therefore, proliferation potential and other cardiac phenotype of these cells will be inherently present in the cells disclosed by cited reference. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established.

New-Necessitated by claim amendments-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following 102 rejections are necessitated by Applicants' amendment to the extent claims now embrace cells being in plurality of EB a limitation that was not previously recited and considered, therefore, this rejection is proper.

Claims 176-181, 196-199 are rejected under 35 U.S.C. 102(a) as being anticipated by Itskovitz-Eldor et al (WO 00/70021, published 11/23/2000).

Itskovitz-Eldor discloses obtaining at least one human-derived embryoid body (hEB), comprising (a) providing human embryonic stem (hES) cells; (b) growing the hES cells in vitro in a vessel under conditions in which said cells undergo differentiation and the cells or aggregates thereof do not adhere to the vessel wall; and (c) incubating for a time sufficient to develop hEBs from said cells. Itskovitz-Eldor also teach conditions whereby the hES undergo differentiation include the absence of inhibitors of differentiation such as leukemia inhibitory factor and fibroblast growth factor. It is noted that Itskovitz-Eldor et al also disclose hEB comprising mesoderm, ectoderm and endoderm lineage cells comprising cells displaying characteristics of cardiac cells (See claims 1-8 and example 4). Thus, Itskovitz-Eldor et al taught an *in vitro* culture of human cell being in plurality of EBs.. The cited reference also exemplified one EB from the plurality of population of EB having cardiac specific synchronous rhythmic activity. The cardio specific linage of human cell disclosed by Itskovitz-Eldor and those embraced by the instant claims appear to be structurally same, therefore, proliferation potential and other cardiac phenotype of these cells will be inherently present in the cells disclosed by cited reference. It is noted that declaration does not provide evidence that other EBs in H9 clone of hES cells would not have cardiac phenotype. MPEP 2113 states "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). Accordingly, Itskovitz-Eldor et al anticipate claims 176-181, 196-199.

Claims 176-181, 196-199 are rejected under 35 U.S.C. 102(e) as being anticipated by Benvenisty (US Patent 7045353, dated 5/16/2006, effective filing date 8/1/2000).

Benvenisty discloses a method for directed differentiation of human embryonic cells to a specific cell type, including the steps of (a) permitting a population of embryonic stem cells to form embryoid bodies; (b) dissociating the embryoid bodies to provide embryonic cells for differentiating in the presence of at least one exogenous factor for an effective period of time; and (c) causing directed differentiation of human embryonic cells to form the specific cell type including heart cells. It is noted that Benvenisty teaches an *in vitro* culture of human cell being in plurality of EBs and also discloses use of exogenous factor to direct differentiation of EBs of cells of specific linage including heart. Since cells of cardiac phenotype in EBs disclosed by Benvenisty and those disclosed in the instant application, appears to be same, therefore, proliferation potential and other cardiac phenotype of these cells will be inherently present in the cells disclosed by cited reference. MPEP 2113 states "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). Accordingly, Benvenisty et al anticipate claims 176-181, 196-199.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 176-181 remain rejected under 35 U.S.C. 103(a) and newly added claims 196-199 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Itskovitz-Eldor et al (Mol Med. 2000; 6(2):88-95, IDS) and Igelmund et al (Pflugers Arch. 1999 Apr;437(5):669-79).

Itskovitz-Eldor et al teach induction of expression of cell-specific genes during differentiation of the human ES cells into embryoid bodies (EB). It is noted that Itskovitz-Eldor et al disclose differentiation of human ES cell in myocardial linage that is induces development of pulsing muscle in EB (see page 92, col. 2, para 2). Itskovitz-Eldor et al also disclose a large vacuolated EB including cardiac muscle cell layer that is pulsing in synchronous rhythm (see Figure 4 A and B). It is further noted that Itskovitz-Eldor further characterizes the differentiated ES cell by dissociating EB with trypsin and plated cell on monolayer. Since, Itskovitz-Eldor et al taught an in vitro culture of human cell of cardio specific linage obtained from human ES cell that shows the cardiac specific synchronous rhythmic activity. The cardio specific linage of human cell disclosed by Itskovitz-Eldor and those embraced by the instant claims appear to be structurally same, therefore, proliferation potential and cardiac phenotype of these cells will be inherent property of the cells. Where the claimed and prior art products are identical or substantially identical in

structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior ad products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433. However, Itskovitz-Eldor et al do not explicitly teach a method to culture cell in contact with a multi electrode array for monitoring cardiac electrical activity.

Prior to instant invention, Igelmund et al (Pflugers Arch. 1999 Apr; 437(5): 669-79) teach a method to investigate the spontaneous electrical activity of cardiomyocyte clusters in EBs, of small groups of cells, and of single cardiomyocytes (see page 670, col. 1, lines 2-4). Igelmund et al disclose that single embryoid bodies are plated for multiple recording from several locations of individual EBs (Figure 1). The electrode matrix consisted of 60 TiN-coated gold electrodes with a diameter of 10 or 30 µm, arranged in eight columns and eight rows with a distance of 100 or 200 µm between adjacent electrodes (see Figs. 4, 5) (see page 670, column 1, extracellular recording section). Igelmund et al teach that by recording population action potentials from the beating areas of EB, one could determine the electrical interaction between cardiomyocytes and beating activity (see page 677, paragraph 2). Igelmund et al conclude that this method of field potential recordings from clusters of ES cell-derived cardiomyocytes within EBs provide a useful tool for studying in vitro chronotropy and action potential propagation (see page 678, column 1, paragraph 2). However, Igelmund et al do not explicitly teach recording action potential of human cells.

Accordingly, in view of the teachings of Igelmund et al and Itskovitz-Eldor, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the method of Igelmund et al by replacing the mouse ES cells to human cells disclosed by Itskovitz-Eldor in order to determine the electrical interaction between cardiomyocytes and beating activity of human cardiomyocytes. Igelmund had already taught a method to use multiple recording from several locations of individual EBs using electrode matrix to determine the action potential from the beating areas (*supra*). In addition, at the time of filing of this application cardiomyocytes differentiated from embryonic stem cell of different species were also known in the art as taught by Itskovitz-Eldor and Igelmund et al and discussed above. One of ordinary skill in the art would be motivated to replace the mouse cells with human cell since, action potential recordings from clusters of ES cell-derived cardiomyocytes within EBs would have provided in vitro chronotropy and action potential propagation of these cells for their potential use in transplantation medicine.

One who would practiced the invention would have had reasonable expectation of success because Igelmund et al had already taught the method of extracellular recordings of the population action potentials of cardiomyocyte clusters to perform long-term recordings (for up to several weeks) from individual EBs under cell culture conditions. Itskovitz-Eldor taught human cardiomyocytes linage cells that are obtained from human ES cell showing cardiac phenotype. Igelmund et al had had already described the use of multiple electrode array system to map the beating area of EBs with electrical activity. Thus, it would have only required routine experimentation to replace the mouse cell with human cardiomyocytes obtained from human ES cell to determine the action potential of pulsating cardiomyocytes as disclosed by Itskovitz-Eldor.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments filed on April 19, 2007 have been fully considered but they are not fully persuasive. Applicants in their argument point out that claims have been amended to recite in vitro culture of isolated human cell being in plurality of EBs. In addition, Applicants argue that Igelund et al do not explicitly teach recording action potential of human cell and presently claimed invention is not rendered obvious for the reasons discussed under 102 rejection.

In response it is noted that claim 176 has been amended to an *in vitro* culture of an isolated human cell being in plurality of EB wherein said EB showing at least one cardiac phenotype. Contrary to applicant's argument cited references teach in vitro hES culture in suspension in order to form plurality of EBs. The specification also teaches that twenty days after initiation of cellular aggregation 20–90% of the structures formed cystic EBs (Fig. 1B-I). Thus, it is apparent that contrary to applicant's argument cited reference teaches an isolated human cells being in plurality of cystic EB's. Furthermore, art also discloses rhythmic pulsation in "minority" of the cystic hEBs (see page 92, col. 2, para. 2, line7-8, emphasis added). It is emphasized the minority is defined as the smaller in number of two groups constituting a whole (see m-w.com/.). Examiner would agree with cited reference

exemplified only one pulsing embryoid body, but clearly did not exclude cardiac phenotype in other population of EBs. The declaration fails to establish the fact that H9 clone of hES cells disclosed in cited reference contained only one EB showing cardiac phenotype.It appears that Applicant is arguing that the cited references do not expressly suggest the claimed invention. However, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. Furthermore, It is also well established that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988). In the instant case, only minority" of the cystic hEBs showed cardiac phenotype, it would have been obvious to one of ordinary skill in the art to use the method disclosed by Igelmund particularly since he had already taught a method to use multiple recording from several locations of individual EBs using electrode matrix to determine the action potential from the beating areas from individual EBs under cell culture conditions. The cells being in plurality (of EBs disclosed by Itskovitz-Eldor et al cell, and cells disclosed by cited reference exemplifying a EB from the plurality of population of EB having cardiac specific synchronous rhythmic activity appear to be structurally same, therefore, proliferation potential and other cardiac phenotype of these cells will be inherently present in the cells disclosed by cited reference. Thus, it would have obvious for one of ordinary skill in the art to try the method of Igelmund to use multiple recording from several locations of individual EBs disclosed by Itskovitz-Eldor using electrode matrix to determine the action potential from the beating areas with reasonable expectation of success in achieving

predictable results. Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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